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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/171,928	10/05/1998	NORIO INOMATA	001560-336	8658

21839 7590 06/03/2004

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/171,928	INOMATA ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Amendment filed 02/19/2004 is acknowledged. Claims 11,21 are amended. Claims 8-11,21 are currently pending.

Claim Rejections - 35 USC § 112, first paragraph.

2. Claims 8-11,21 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cardiac hypertrophy is rats using ANP at dosages which do not cause hypertensive or diuretic effect, does not reasonably provide enablement for (1) treatment of cardiac hypertrophy with ANP in species other than rats at dosages which do not cause diuretic and hypotensive effects; (2) treatment of cardiac hypertrophy with agents other than ANP at dosages which do not cause diuretic and hypotensive effects. The rejection is maintained for the reasons of record and further in view of the following.

Applicant argues that rat model is well excepted model of hypercardia in humans. Examiner agrees that it might be so for the mechanisms of development of hypercardia. However, at issue is not the interspecies differences or similarities in the etiology of the disease but rather whether the mechanism of action of ANP is the same. The question remains whether ANP is capable of acting without causing diuretic

and hypotensive effects in humans (or other species). Applicant cites references which allegedly demonstrate similarity of receptors (e.g., reference of Suga et al cited on p. 7, bottom, of the response). However, similarity of receptors does not indicate that the signal transduction mechanisms mediated by the receptors and the resulting physiological effect will be the same on different species. For example, applicants themselves were arguing not to consider reference of Blaine et al used in the art rejection because it teaches diuretic effect. At the same time, the dosages of ANP used in Blaine on hamsters are of the same range as the dosages used in the example 3 in this specification on rats - see discussion of the dosages on p. 7, Office action mailed October 9, 2002. Further, applicants argued in the response filed 07/25/2002 that the finding of the effect of ANF without involving hypotensive and diuretic effect is unexpected and unusual. Hence, the examiner has reasons to believe that effect of the same agent, namely ANP might be different in different species, and maintains that since the art is deemed unpredictable in regard to ANP acting without involving hypotensive and diuretic effects, and in the absence or working examples and sufficient guidance, specification does not commensurate with the scope of invention claimed.

As for the second part of the rejection, Examiner emphasizes that, again, the issue is not the similarity of known effects between various natriuretic peptide receptor

ligands, but whether these different ligands will be capable of acting without causing diuretic and hypotensive effects. Applicant discusses other effects known to be similar, but does not present facts that other agent, BNP for example, are capable of causing diuretic and hypotensive-free effect as ANP. Further, to demonstrate that even for ANP, ANP species of different origin may have different effect, applicant's attention is directed to reference of Squadrito, (PubMed ID: 2473344, 1989) which shows difference of cerebral effects of ANP derived from human and rat.

Claim Rejections - 35 U.S.C. § 102 and 103.

3. In view of amendment to the claims removing the claim language requiring removal of pulmonary congestion to be the causative effect, examiner returns to rejection under 35 U.S.C. 102(b).

4. Claims 8-11, 21 are rejected under 35 U.S.C. 102(b) as anticipated by Blaine et al. (US Patent 4652549) as evidenced by Espiner[1].

[1]Note that, although the date of the "Espiner" reference is later than the priority date of the instant application, the reference is a review describing studies preceding the instant application; the reference is used merely to demonstrate well known mechanisms of action.

Blaine teaches method of treatment of cardiac hypertrophy using continuous administration of atrial natriuretic peptide (ANF) and fragments thereof. See abstract, summary, claims 1-8. The method step in Blaine, administration of ANF in anti-cardiac hypertrophy amounts, is the same as in the instantly claimed method. Further, the amount of ANF (or its analogs) in Blaine appears to be substantially lower that in the instant method: The dosage of ANF administered to hamsters, mice and rats in the referenced method is in amount of from about 10 to about 2000 picomoles/kg/min. If recalculated into the units used to describe the instant method, μg/kg/min, the referenced concentrations are equivalent to 0.00003 to 0.07 μg/kg/min [2]. The lower limit of this range is several orders less then 0.1 μg/kg/min used for same animals in the instant method, and the upper limit is about the same as in the instant method. Note that applicant asserts, contrary, that amounts of ANF used in the instant method are lower than those used in the prior art.

In regard to claim language "in amount effective for reducing pulmonary congestion", as pulmonary congestion arises from cardiac hypertrophy, treatment of the latter will also treat the former.

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[2] For recalculation, Examiner used the notion in the specification (p. 17, last line) that 426±53 pg/ml ANF is approximately 0.14 nM)

Further, it is well known that ANF, as well as its analogs, stimulate guanylate cyclase A and production of cGMP. See, e.g., Espiner, p. 205, last paragraph. Therefore, these claimed effects of ANF are inherently present. As for the claim limitation "amount... not effective for diuretic and hypertensive effects", the reference is silent about the presence of such effects of ANF. Demonstration of reduction in water content described in the reference does not amount to demonstration of a diuretic effect (as was asserted by applicant). Note that prior art acknowledges that, first, natriuretic peptides have a wide range of actions, and, second, hypertrophy is a result of an interaction between a variety of different interrelated signaling pathways. See, for example, Espiner, p. 205, right column, lines 30-33. Therefore, it is not possible to discern which particular mechanism was engaged in achieving an overall effect of treatment. Even though separate mechanisms might have been demonstrated in specifically designed model conditions, Examiner assumes that the referenced method inherently included the effect as instantly claimed. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on applicant to show that the referenced method did not include the effect as instantly claimed. So far applicant provided arguments about potential differences in the mechanisms of action of ANF in the claimed and referenced methods, but did not provide a clear demonstration that 10-2000 picomoles/kg/min

of ANF used in the reference do not have the effect as instantly claimed, or that the effect of the referenced concentration is exclusively limited to diuretic/natriuretic action.

Therefore, the referenced method anticipates the instantly claimed method of treatment of heart disease based on hypertrophy comprising administration of a substance that acts on natriuretic receptor, guanylyl cyclase A and is able to accelerate production of cGMP.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date

of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

May 28, 2004

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

mlb